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Date: February 1, 2008 Rebecca A. Bellas

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Applicant(s): Kusama, *et al.*

Serial No: 10/826,119

Filing Date: April 16, 2004

Examiner: Suryaprabha Chunduru

Art Unit: 1637

Title: OLIGONEUCLEOTIDE SEQUENCES THAT IDENTIFY SPECIES OF ANIMAL

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
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APPEAL BRIEF

Dear Sir:

Appellants' representative submits this brief in connection with an appeal of the above-identified patent application. In the event any additional fees may be due and/or are not covered by the credit card, the Commissioner is authorized to charge such fees to Deposit Account No. 50-1063.

I. Real Party in Interest (37 C.F.R. §41.37(c)(1)(i))

The real party in interest in the present appeal is National Institute of Agrobiological Sciences (Japan) and Incorporated Administrative Agency Fertilizer and Feed Inspection Services (Japan), the assignees of the present application.

II. Related Appeals and Interferences (37 C.F.R. §41.37(c)(1)(ii))

Appellants, appellants' legal representative, and/or the assignee of the present application are not aware of any appeals or interferences which may be related to, will directly affect, or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. Status of Claims (37 C.F.R. §41.37(c)(1)(iii))

Claims 1-23, 26-34, and 36-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected Group. Claims 24-25 and 35 stand rejected by the Examiner. The rejection of claims 24-25 and 35 is being appealed.

IV. Status of Amendments (37 C.F.R. §41.37(c)(1)(iv))

No claim amendments have been made subsequent to the Final Office Action dated July 6, 2007. The last amendments to the claims occurred in a Supplemental Preliminary Amendment mailed to the USPTO on October 5, 2004.

V. Summary of Claimed Subject Matter (37 C.F.R. §41.37(c)(1)(v))

Independent Claim 24

Independent claim 24 relates to a primer pair useful in detecting the presence of ruminant DNA. The primers are complementary to regions on or near a mitochondrial gene coding for ATP synthase 8 (ATPase8). The primer pair is a combination of the DNA sequence of SEQ ID NO:3 and SEQ ID NO:4 or a combination of sequence ID NO:5 and SEQ ID NO:6. (*See*, for example, Examples 2 and 3, pages 16-18, and

Figure 6).

Independent Claim 35

Independent claim 35 relates to a kit for the detection of animal-derived component present in a sample. The kit comprises a primer pair useful in detecting the presence of ruminant-derived DNA.

VI. Grounds of Rejection to be Reviewed (37 C.F.R. §41.37(c)(1)(vi))

A. Whether claims 24-25 and 35 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Saulle et al (*Journal of Animal Science*, vol. 77, p. 3389, 1999) in view of Lowe et al (*Nucleic Acid Research*, vol. 18, p. 1757, 1990)?

VII. Argument (37 C.F.R. §41.37(c)(1)(vii))

A. Rejection of Claims 24-25 and 35 Under 35 U.S.C. §103(a)

Claims 24-35 and 35 have been rejected under 35 U.S.C. §103(a) over Saulle et al in view of Lowe et al.

Saulle et al relates to mitochondrial genes encoding ATPase8 from species of chamois, alpine ibex, and red deer. Specifically, Saulle et al merely teaches a nucleic acid sequence of a region encoding ATPase8. However, this region is relatively variable between animal species. Saulle et al further teaches that a relatively conserved portion is present within the region encoding ATPase8. Lowe et al merely discloses a computer program for rapid selection of preferable primers for polymerase chain reaction (PCR) to amplify a single target sequence effectively. The Examiner contends that one skilled in the art would have used the software of Lowe et al on the genes of Saulle et al to generate primers, and thus render the invention obvious.

a. Summary of the Invention

The claims are directed toward primer pairs that amplify ATPase8 gene sequences found in mitochondrial DNA originating from ruminants while having significantly reduced ability to amplify ATPase8 gene sequences originating from other animals. The ATPase8 gene is highly homologous between animal species and primers directed toward ATPase8 are expected to amplify all animal-derived ATPase8 genes. The Application discloses primers that have affinity for ATPase8 gene sequences from a broad spectrum of animal species. The claims are directed toward primer pairs that target specific subclasses of animals, such as ruminants, have been carefully engineered.

b. The cited art does not teach comparing multiple DNA sequences as a factor in primer design.

In order to identify a primer to detect DNA derived from a ruminant, it is required that the primer has (i) a specific portion of the entire genome sequence, (ii) a specific length of the sequence, and (iii) a specific combination of these sequences. Saulle et al does not teach or suggest that the ruminant deer sequence can satisfy the three above mentioned requirements for the primer. And in order to run the computer program as disclosed by Lowe et al, one skilled in the art must have selected a specific region (i.e. target sequence) amplified by a specific primer pair for detection of ruminant DNA. Consequently, even though Saulle et al discloses the complete nucleic acid sequence to be detected, one skilled in the art would NOT have selected (i) a specific portion of the entire genome sequence, (ii) a specific length of the sequence, and further (iii) a specific combination of these sequences.

As long as the target sequence to be amplified cannot be selected appropriately, even if the known nucleic acid sequence of Saulle et al is combined with the step of

generating and designing primers as taught by Lowe et al, the specific combination of primers of the claimed invention could not be obtained by those skilled in the art. In other words, one skilled in the art would not have expected to obtain primers capable of discriminating between homologous sequences without extensive experimentation to determine which primers actually perform as desired in PCR. This is because Saulle et al does NOT teach or suggest whether or not the ruminant DNA can be actually detected without detecting DNAs other than the ruminant DNA.

Furthermore, one skilled in the art would not have been able to generate the claimed primers using the software of Lowe et al in combination of the sequence disclosed by Saulle et al for these additional reasons.

Saulle et al does NOT teach or suggest primers that discriminate between homologous ATPase8 targets. The software of Lowe et al generates possible primers from a single user inputted target DNA sequence by optimizing GC content, GC bases present at the 3' end, length of amplification product, contiguous base pair homology, and annealing temperature of possible primers. Therefore, while one skilled in the art might conceivably expect Saulle et al to be useful in generating primers capable of amplifying an ATPase8 target, none of the optimization steps of Lowe et al indicates that such primers can discriminate between two homologous ATPase8 targets.

In order to have a reasonable expectation of designing primers that can discriminate between two homologous ATPase8 targets, it is necessary to compare the desired DNA target or targets with homologous undesired target or targets. For example, Fig. 5 shows the ability of the anicon5 and anicon3 primer pair to detect mammalian DNA targets including non-ruminants pig, horse, rabbit and whale. Fig. 6 shows the ability of the rumicon5 and rumicon3 primer pair to detect ruminant DNA targets while distinguishing non-ruminants pig, horse, rabbit and whale. The software of Lowe et al does not have the functionality to design a primer with the discrimination of the rumicon5 and rumicon3 primer pair for at least the reason that designing such primers requires comparing several DNA sequences.

To briefly restate, the software of Lowe functions by the user imputing a single target DNA sequence. The software then proceeds to do a series of optimization calculations to determine appropriate primer pairs to amplify that single, individual target. However, one having ordinary skill in the art would also expect the majority of the generated primer sequences to be significantly complementary to DNA sequences that are highly homologous to the inputted sequence.

For example, if a user imputed the DNA sequence for Red Deer ATPase8, disclosed by Saulle et al, into the program of Lowe, a person having ordinary skill would expect a significant degree of amplification using the generated primers with the homologous DNA sequences found in horses, pigs, chickens, ect. The list of primer sequences outputted by the program of Lowe will give no indication of which primer pairs would show significant cross-reactivity with other homologous DNA sequences and which ones would not. The only way such information can be theoretically obtained is to compare the DNA primers generated from the single inputted target sequence to a second, third, fourth, fifth, ect. homologous DNA sequence of known identity and to calculate the likelihood of the generated primers to prime the homologous DNA sequences. The ability to compare primers to MULTIPLE homologous DNA sequences is a function that the program of Lowe does not have.

Since the program of Lowe does not have the functionality required to generate primers capable of discriminating between ruminants and non-ruminants, it is respectfully requested that the rejection of claims 24-25 and 35 under 35 USC § 103 be withdrawn.

c. The cited art does not teach the multiple DNA sequences that are required to design primers capable of selecting between ruminants and non-ruminants.

Construction of primer pairs to amplify any random DNA sequence successfully typically involves optimizing GC content, GC bases present at the 3' end, length of amplification product, contiguous base pair homology, and annealing temperature of

possible primers in light of the temperature conditions typically employed in PCR. Such calculations are admitted basic and can typically be done by a person having skill in the art via manual calculation.

As discussed in the above section, any primer pair that is calculated to be useful in amplifying a desired target must be compared to homologous, undesired targets to ascertain if the primer pair will be selective between the desired target and an undesired, homologous target. The design of a successful discriminating primer pair relies on the recognition of minute differences between homologous sequences. The cited art does not disclose homologous, undesirable ATPase8 gene sequences necessary to design primers having discrimination ability. Saulle et al discloses the ATPase8 gene sequence for three ruminant species. However, in order to design a primer having the ability to discriminate between ruminants and non-ruminant species, the DNA sequences of non-ruminant species needs to be known as well.

The need for the comparison of multiple DNA sequences to achieve discriminating ability was indicated by the Examiner in the Advisory Office Action dated October 2, 2007. The Examiner states, "there is express suggestion in the prior art to design a primers from a known target sequence and Lowe et al. explicitly taught that all primers designed for the over 10 gene products were experimentally tested and the results showed that all the amplification products specified by the primers are of the predicted size." (emphasis added) The Examiner quite correctly states that primers designed by the program of Lowe may be expected to work all the time. However, the crux of designing a discriminating primer pair is that the primers will not work all the time. The discriminating primer will work on certain sequences but will not work on certain other homologous sequences.

We suspect that the Examiner is reasoning under the assumption that a user can input the gene sequence of, for example, Red Deer ATPase8, into the Lowe program and that the primers will work for Red Deer and for no other sequences. A user can then enter the gene sequence for other desired species and obtain similar results, and hence, discriminating primers with little or no experimentation. This is a logical fallacy

and Lowe et al provides no support for this fallacy. The 10 gene products/sequences referred to by the Examiner in Lowe are for completely different non-homologous genes, for example, preproendothelin, superoxide dismutase, retinoblastoma susceptibility gene, ect. (Lowe et al, pp.1759-60, Lowe et al does not list all 10 gene sequences used). There is no mention in Lowe et al of a primer designed for one gene being tested on another gene as a target. That is, for example, attempting to amplify a superoxide dismutase gene using a primer designed for preproendothelin. Such an experiment is not expected to be attempted since there is no expectation of any individual primer pair working on such dissimilar targets. However, the lack of such an experiment is evidence that Lowe contains no teaching regarding the cross-reactivity of primer pairs in PCR.

Similarly, Lowe et al does not report, for example, the ability of a primer pair designed for the superoxide dismutase gene from Species A to work on the superoxide dismutase gene from Species B or Species C or Species D, ect. The absence of experiments of this kind in Lowe et al means that Lowe et al has no teachings regarding the ability of the disclosed program to design primers to select between targets that are the same type of gene but from different species. Genes coding for the same protein, but from different species, are typically highly homologous, especially when the gene is a basic component of the cellular respiratory machinery of all cells in the animal kingdom, and hence, any mutation in that gene impairing function will result in a non-viable organism. The homology of the ATPase8 gene between species is well-documented in the Application.

The fact that primers can and do have the ability to prime homologous sequences, even where the primer pair and the target are not 100% complementary in base pairing, is fundamental knowledge in molecular biology, which we suspect the Examiner may be overlooking. This phenomenon can be seen, for example, in Figure 6 of the Application. When PCR is conducted using ruminant specific primers and ruminant DNA target, a homogeneous product with the specific size of the ATPase8 gene product is obtained. When, a non-ruminant DNA target is substituted in the PCR

reaction, the specific size of DNA indicating the gene product of ATPase8 is not obtained showing the ability of the ruminant specific primers to discriminate between homologous sequences. There is some literature that describes discrimination between specific, individual animal species, such as between pig and cattle. However, in the present invention, the target to be detected is not a specific animal species but rather a group of ruminants that includes multiple species, for example, cattle, sheep, goat, and deer. Thus, the applicants are unaware of any literature that demonstrates discrimination between a group of species, such as ruminants, from other groups. Therefore, the discrimination properties of the disclosed primers are novel. Again, Lowe et al does not contain any indication that the program disclosed is capable of generating primers able to discriminate between species or between groups of species, or more specifically, primers that amplify some sequences but not other homologous sequences.

Even monoclonal antibodies that recognize the complicated, tertiary biological structures of proteins are known to be cross-reactive with homologous proteins. Hence, a vaccination against flu strain A can still provide partial immunity to flu strain B. The principle is greatly magnified when the basis for recognition is reduced to a mere primary sequence of base pairs without any secondary or tertiary structure, as is the case with PCR. In order to design a primer pair capable of discriminating between homologous sequences, information regarding the undesirable, homologous sequences needs to be supplied. Here, the cited art fails to provide the needed information and fails to establish how to use that information, even if available, to (i) select a specific portion of the entire genome sequence, (ii) select a specific length of the sequence, and (iii) select specific combination of these sequences to arrive at the claimed invention, all the foregoing being elements needed to design a discriminating primer pair.

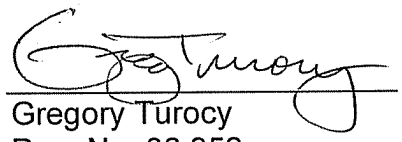
In fact, there is a possibility that it will be impossible to design a discriminating primer pair in situations where the homology between the desired target and the undesired target is too great; therefore, there is no expectation of being successful in discriminating between homologous species by PCR in general. Specifically, all

possible primers that are 100% homologous to the desired target (or even non-100% homologous) may also prime some undesired targets and form a product that cannot be distinguished on an agarose gel. Further, it may be impossible to find a non-100% homologous primer pair that both primes the target sequence and does not prime undesired targets.

d. Conclusion.

For at least the above reasons, the claims currently under consideration are believed to be patentable over the cited art. Therefore, it is respectfully requested that the rejections of claims 24, 25, and 35 under 35 U.S.C. 103 be withdrawn.

Respectfully submitted,
AMIN, TUROCY & CALVIN, LLP



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VIII. Claims Appendix (37 C.F.R. §41.37(c)(1)(viii))

1. (withdrawn, original) A method for identifying animal species comprising:

amplifying a DNA sequence by PCR using a DNA in a sample as a template and animal-specific DNA sequences as a primer pair, wherein the animal-specific DNA sequences are derived from a ATP synthase subunit 8 gene or a region proximal thereto of a mitochondrial genome, and

detecting the amplified DNA sequence.

2. (withdrawn, original) The method of claim 1, wherein the animal is a mammal.

3. (withdrawn, original) The method of claim 2, the mammal is selected from the group consisting of cattle, sheep, goat, deer, pig, horse, rabbit, and whale.

4. (withdrawn, previously presented) The method of claim 2, wherein the primer pair is a combination of the DNA sequence of SEQ ID NO: 1 and the DNA sequence of SEQ ID NO: 2.

5. (withdrawn, original) The method of claim 1, wherein the animal is a ruminant.

6. (withdrawn, original) The method of claim 5, the ruminant is selected from the group consisting of cattle, sheep, goat, and deer.

7. (withdrawn, previously presented) The method of claim 5, wherein the primer pair is a combination of the DNA sequence of SEQ ID NO: 3 and the DNA sequence of SEQ ID NO: 4, or a combination of the DNA sequence of SEQ ID NO: 5 and the DNA sequence of SEQ ID NO: 6.

8. (withdrawn, original) The method of claim 1, wherein the animal is a cattle.

9. (withdrawn, original) The method of claim 8, wherein the primer pair is a combination of DNA sequences selected from the group consisting of the following DNA sequence combinations: SEQ ID NO: 9 and SEQ ID NO: 13; SEQ ID NO: 9 and SEQ ID NO: 12; SEQ ID NO: 11 and SEQ ID NO: 13; SEQ ID NO: 10 and SEQ ID NO: 12; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 8 and SEQ ID NO: 12; and SEQ ID NO: 14 and SEQ ID NO: 15.

10. (withdrawn, original) The method of claim 1, wherein the animal is a pig.

11. (withdrawn, original) The method of claim 10, wherein the primer pair is a combination of the DNA sequence of SEQ ID NO: 17 and the DNA sequence of SEQ ID NO: 19, or a combination of the DNA sequence of SEQ ID NO: 18 and the DNA sequence of SEQ ID NO: 22.

12. (withdrawn, original) The method of claim 1, wherein the animal is a sheep.

13. (withdrawn, original) The method of claim 12, wherein the primer pair is a combination of the DNA sequence of SEQ ID NO: 23 and th DNA sequence of SEQ ID NO: 24.

14. (withdrawn, original) The method of claim 1, wherein the animal is a goat.

15. (withdrawn, original) The method of claim 14, wherein the primer pair is a combination of the DNA sequence of SEQ ID NO: 25 and the DNA sequence of SEQ ID NO: 26.

16. (withdrawn, original) The method of claim 1, wherein the animal is a chicken.

17. (withdrawn, original) The method of claim 16, wherein the primer pair is a combination of the DNA sequence of SEQ ID NO: 28 and the DNA sequence of SEQ ID NO: 30.

18. (withdrawn, original) The method of claim 1, wherein the animal is a fish.

19. (withdrawn, original) The method of claim 18, the fish is selected from the group consisting of sardine, flatfish, salmon, Alaska Pollack, tuna, and lady crab.

20. (withdrawn, previously presented) The method of claim 18, wherein the primer pair is a combination of the DNA sequence selected from the group consisting of SEQ ID NOS: 32, 34, 38 and 39 and the DNA sequence selected from the group consisting of SEQ ID NOS: 33, 35, 36, 37, 40, and 41.

21. (withdrawn, previously presented) The method of claim 1, wherein the sample is selected from a group consisting of raw meat, raw fish, processed meat food products, processed fish food products, food products containing processed meat, food products containing processed fish, blood, hair, body fluids, milk, milk processing products, meat and bonemeal, bonemeal, fishmeal, fish soluble, and feed, fertilizer, and feed additive containing them.

22. (withdrawn, original) A primer pair for detection of a mammal-specific DNA, the primer pair being a combination of the DNA sequence of SEQ ID NO: 1 and the DNA sequence of SEQ ID NO: 2.

23. (withdrawn, original) The primer pair of claim 22, the mammal is selected from the group consisting of cattle, sheep, goat, deer, pig, horse, rabbit, and whale.

24. (original) A primer pair for detection of a ruminant-specific DNA, the primer pair being a combination of the DNA sequence of SEQ ID NO: 3 and the DNA sequence of SEQ ID NO: 4, or a combination of the DNA sequence of SEQ ID NO: 5 and the DNA sequence of SEQ ID NO: 6.

25. (original) The primer pair of claim 24, the ruminant is selected from the group consisting of cattle, sheep, goat, and deer.

26. (withdrawn, original) A primer pair for detection of a cattle-specific DNA, the primer pair being a combination of DNA sequences selected from the group consisting of the following DNA sequence combinations: SEQ ID NO: 9 and SEQ ID NO: 13; SEQ ID NO: 9 and SEQ ID NO 12; SEQ ID NO: 11 and SEQ ID NO: 13; SEQ ID NO: 10 and SEQ ID NO: 12; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 8 and SEQ ID NO: 12; and SEQ ID NO: 14 and SEQ ID NO: 15.

27. (withdrawn, original) A primer pair for detection of a pig-specific DNA, the primer pair being a combination of the DNA sequence of SEQ ID NO: 17 and the DNA sequence of SEQ ID NO: 19, or a combination of the DNA sequence of SEQ ID NO: 18 and the DNA sequence of SEQ ID NO: 22.

28. (withdrawn, original) A primer pair for detection of a sheep-specific DNA, the primer pair being a combination of the DNA sequence of SEQ ID NO: 23 and the DNA sequence of SEQ ID NO: 24.

29. (withdrawn, original) A primer pair for detection of a goat-specific DNA, the primer pair being a combination of the DNA sequence of SEQ ID NO: 25 and the DNA sequence of SEQ ID NO: 26.

30. (withdrawn, original) A primer pair for detection of a chicken-specific DNA, the primer pair being a combination of the DNA sequence of SEQ ID NO: 28 and the DNA sequence of SEQ ID NO: 30.

31. (withdrawn, original) A primer pair for detection of a fish-specific DNA, the primer pair being a combination of the DNA sequence selected from the group consisting of SEQ ID NOS: 32, 34, 38 and 39 and the DNA sequence selected from the group consisting of SEQ ID NOS: 33, 35, 36, 37, 40, and 41.

32. (withdrawn, original) The primer pair of claim 31, the fish is selected from the group consisting of sardine, flatfish, salmon, Alaska Pollack, tuna, and lady crab.

33. (withdrawn, original) A primer pair for detection of a plant-specific DNA, the primer pair being a combination of the DNA sequence of SEQ ID NO: 42 and the DNA sequence of SEQ ID NO: 43.

34. (withdrawn, original) A method for detecting animal-derived components present in mixed feed comprising:

amplifying a DNA sequence by PCR using a DNA in a sample as a template and animal-specific DNA sequences as a primer pair, wherein the animal-specific DNA sequences are derived from a ATP synthase subunit 8 gene or a region proximal thereto of a mitochondrial genome, and

detecting the amplified DNA sequence.

35. (previously presented) A kit for detecting an animal-derived component present in a sample comprising: at least one primer pair selected from the group consisting of the following DNA sequence combinations: SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 5 and SEQ ID NO: 6; SEQ ID NO: 9 and SEQ ID NO: 13; SEQ ID NO: 9 and SEQ ID NO: 12; SEQ ID NO: 11 and SEQ ID NO: 13; SEQ ID NO: 10 and SEQ ID NO: 12; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 8 and SEQ ID NO: 12; SEQ ID NO: 14 and SEQ ID NO: 15; SEQ ID NO: 17 and SEQ ID NO: 19; SEQ ID NO: 18 and SEQ ID NO: 22; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 28 and SEQ ID NO: 30; and a combination of a DNA sequence selected from the group consisting of SEQ ID NOS: 32, 34, 38, and 39, and a DNA sequence selected from the group consisting of SEQ ID NOS: 33, 35, 36, 37, 40, and 41.

36. (withdrawn, original) The kit of claim 35, further comprising a primer pair for detection of a plant-specific DNA, the primer pair being a combination of the DNA sequence of SEQ ID NO: 42 and the DNA sequence of SEQ ID NO: 43.

37. (withdrawn, original) A method for detecting plant-derived components present in sample comprising:

amplifying a DNA sequence by PCR using a DNA in a sample as a template and plant-specific DNA sequences as a primer pair, wherein the plant-specific DNA sequences are derived from a ATP synthase submit 8 gene or a region proximal thereto of a mitochondrial genome, and

detecting the amplified DNA sequence.

IX. Evidence Appendix (37 C.F.R. §41.37(c)(1)(ix))

None.

X. Related Proceedings Appendix (37 C.F.R. §41.37(c)(1)(x))

None.